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Effects of β-Adrenoceptor Antagonists on Portal Vein Hypertension and Ethanol-induced Gastric Mucosal Damage in Rats

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Abstract—The effects of various β-adrenoceptor antagonists, with different pharmacological properties, on systemic and portal vein blood pressure and on ethanol-induced gastric mucosal damage were examined in surgically-induced portal hypertensive rats. Propranolol (5, 10 or 20 mg kg^{-1}), nadolol (5 or 10 mg kg^{-1}), metoprolol (10 or 20 mg kg^{-1}), labetalol (20 or 40 mg kg^{-1}) and pindolol (3 or 6 mg kg^{-1}) reduced systemic blood pressure to a similar degree in both portal vein-ligated and sham-operated rats. All β-adrenoceptor antagonists, except for pindolol, significantly reduced portal venous pressure and ethanol-induced macroscopic gastric mucosal damage in portal hypertensive animals. Sham-operated rats had lower portal venous pressure and less gastric damage compared with portal hypertensive rats, but both were unaffected by β-adrenoceptor antagonist pretreatment. We conclude that: propranolol, nadolol, metoprolol and labetalol are effective in reducing the portal venous pressure and ethanol-induced gastric mucosal damage in portal hypertensive rats, but not in portal normotensive animals; there was no direct relationship between the reduction of portal vein and systemic blood pressure; and local anaesthetic action is probably important in reducing the portal vein pressure and ethanol-induced gastric mucosal lesions, while the intrinsic sympathomimetic effect can counteract the actions of the β-adrenoceptor antagonists on portal venous pressure and gastric mucosa.

It has been shown in various studies that portal hypertension predisposes to gastric mucosal lesions (Sarfeh et al 1982, 1984; Dobbs et al 1991; Iwao et al 1992), variceal bleeding and other complications (Van Thiel et al 1980). In animal experiments propranolol has been shown to reduce portal vein pressure and ethanol-induced gastric mucosal damage (Sankary et al 1986). Clinical trials have also confirmed that propranolol and some other β-adrenoceptor antagonists are effective in reducing the portal vein pressure and incidence of upper gastrointestinal haemorrhage in portal hypertensive patients (Hillon et al 1982; Mills et al 1983; Westaby et al 1983; Gatta et al 1985; Olsson 1989). However, the mucosal-protective mechanism of these β-adrenoceptor antagonists is still not well understood (Garcia-Tsao et al 1986; Hosking et al 1987).

In our experiments, we examined the possible mechanisms of action of different β-adrenoceptor antagonists by using drugs with various known modes of action. Table 1 shows the pharmacological properties of various β-adrenoceptor antagonists that we used in the present study (Hoffman & Lefkowitz 1990). These drugs were chosen because each of them differs from propranolol by one property; metoprolol is a β_1-selective agent, nadolol has no local anaesthetic activity, labetalol possesses an additional α-adrenoceptor-antagonizing action, pindolol has partial agonist activity.

Materials and Methods

Induction of portal hypertension and regimen of drug treatment

Male Sprague-Dawley rats, 250–300 g, were used in all experiments. Portal hypertension was induced by partial ligation of the portal vein (Dobbs et al 1991). After ether anaesthesia, a midline incision was made in the upper abdomen. The portal vein was identified and a silk thread was placed around it, close to the hilum of the liver. The portal vein, together with the shaft of a blunted 20 gauge hypodermic needle, were ligated together, occluding all the blood flow in the portal vein. After removal of the needle, a reproducible partial occlusion of the portal vein was produced. Control (sham-operated) rats were operated in exactly the same manner, except that no ligation was made around the portal vein. Experiments were performed 48 h after operation. All rats were fasted for 24 h before experimentation, but were allowed free access to water.

Rats were given one single intraperitoneal injection of the β-adrenoceptor antagonists listed in Table 1. At least two different doses were tested for each drug. No injection was given in one group of rats and isotonic saline (NaCl, 0·9% w/v) was injected in another group as control.

After 30 min, half of the number of rats underwent haemodynamic studies and the other half were given 10 mL kg^{-1}, 50% v/v ethanol intragastrically. The gastric lesions were measured after 1 h.

Haemodynamic studies

The rats were anaesthetized with 50 mg kg^{-1} pentobarbitone given intraperitoneally. Systemic arterial pressure and pulse

Table 1. β-Adrenoceptor antagonists used and their pharmacological properties.

	Selectivity	Partial agonist activity	Local anaesthetic activity	α-Adrenoceptor antagonizing activity
Propranolol	None	None	+++	None
Metoprolol	β_1	None	+	None
Nadolol	None	None	None	None
Labetalol	None	None	++	+
Pindolol	None	+	++	None

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Table 2. Mean blood pressure and pulse rate in portal vein-ligated and sham-operated rats in relation to β-adrenoceptor blockage.

Dose (mg kg^{-1}) Pretreatment (i.p.)		Portal vein-ligated rats: Mean blood pressure (mmHg)	Portal vein-ligated rats: Pulse rate (beats min^{-1})	Sham-operated rats: Mean blood pressure (mmHg)	Sham-operated rats: Pulse rate (beats min^{-1})
No injection		88±3	302±12	95±3	322±18
Saline		87±3	308±4	91±2	306±9
Propranolol	5	64±6*	250±11**	64±2*	257±7**
	10	57±3*	238±5**	57±2*	258±9**
	20	48±4*	229±7**	48±1*	236±6**
Nadolol	5	47±1*	231±5**	52±3*	226±5**
	10	49±4*	219±8**	51±3*	223±7**
Metoprolol	10	57±2*	239±7**	53±4*	243±11**
	20	61±4*	254±14**	60±3*	245±5**
Labetalol	20	57±2*	247±7**	54±3*	243±8**
	40	51±3*	242±9**	52±2*	239±9**
Pindolol	3	57±3*	356±11*	58±3*	355±10*
	6	70±4*	352±12*	68±2*	349±10*

*$P<0.01$, **$P<0.001$, compared with the saline-injected group. Results are expressed as mean±s.e.m., n=6.

rate were measured by cannulating the left carotid artery with a polythene tube connecting to a physiograph (Narco Biosystems, MK-IV). Portal venous pressure was measured by inserting a 19 gauge needle into the portal vein proximal to the ligation site. The needle was connected to the same physiograph.

Gastric studies

In conscious rat experiments, animals were given a single oral dose of 50% v/v ethanol via a gastric tube. One hour later, the rats were killed by a single heavy blow on the head. The stomachs were taken out and were dissected along the greater curvature to expose the glandular mucosa. The area of the total glandular mucosa and the areas of gross haemorrhagic necrosis were traced on a glass slide and their sizes were estimated by projecting the tracing onto graph paper. Mucosal necrosis was expressed as the percentage of the total area of the glandular mucosa with gross haemorrhagic lesions.

Statistical analysis

The results were analysed using the two-way unpaired Student's *t*-test. Linear correlations were determined by least regression analysis. $P<0.05$ was regarded as statistically significant.

Results

The results are summarized in Tables 2 and 3. There were no statistically significant differences between the saline-injected group and the group receiving no injection in the four parameters that we measured (mean blood pressure, pulse rate, portal venous pressure and mucosal necrosis). All drug-treated groups were then compared with the saline-injected group.

The systemic blood pressure of all groups of rats were decreased ($P<0.01$) after receiving the β-adrenoceptor antagonists in both portal vein-ligated and sham-operated rats (Table 2). The pulse rates of rats receiving propranolol, nadolol, metoprolol and labetalol were markedly decreased ($P<0.001$), while those receiving pindolol were increased ($P<0.01$) (Table 2).

Portal vein ligation significantly increased the portal vein pressure within two days, and was significantly different from the sham-operated control group (Table 3). In sham-operated rats, the portal vein pressure was unaffected by β-adrenoceptor antagonist pretreatment.

Propranolol, nadolol, metoprolol and labetalol decreased the gastric mucosal necrosis in portal vein-ligated rats. Pindolol did not affect the gastric mucosal damage induced by ethanol in portal hypertensive animals. β-Adrenoceptor antagonist pretreatment did not affect ethanol-induced gastric mucosal lesions in sham-operated rats.

There was no correlation found between systemic blood pressure of individual rats and that in the portal vein. Nor was there any correlation between the degree of fall in systemic blood pressure and in the portal circulation for the specific doses of each of the β-adrenoceptor antagonists.

Discussion

The first part of the experiment (haemodynamic studies) confirms that portal venous pressure was significantly reduced by various β-adrenoceptor antagonists (propranolol, nadolol, metoprolol and labetalol) in portal hypertensive rats, while the portal venous pressure in sham-operated rats remained unchanged. These findings are consistent with the results reported in previous studies (Mills et al 1983; Westaby et al 1983; Gatta et al 1985; Sankary et al 1986). In addition, it was found that labetalol (an α- and β-adrenoceptor antagonist), but not pindolol (a β-adrenoceptor antagonist with intrinsic sympathomimetic activities), produced a similar effect. These findings indicate that not all β-adrenoceptor antagonists have a similar action on portal venous pressure, although they all have the capacity to reduce the systemic blood pressure. Furthermore, the degree of drop in portal venous pressure has no direct relationship with the decrease in systemic blood pressure for each single dose of β-adrenoceptor antagonist used. This phenomenon was further demonstrated by the fact that in rats treated with pindolol (3 and 6 mg kg^{-1}), nadolol (5 mg kg^{-1}) and metoprolol (10 mg kg^{-1}), there was no significant drop in portal venous pressure despite a marked decrease in systemic blood pressure, indicating that the mechanisms involved in the reduction of portal venous and systemic pressures are different.

Table 3. Portal venous pressure and extent of mucosal necrosis in portal vein-ligated and sham-operated rats in relation to β-adrenoceptor blockade.

Dose (mg kg^{-1}) Pretreatment (i.p.)		Portal vein-ligated rats		Sham-operated rats	
		Portal venous pressure (cm H_2O)	Mucosal necrosis (% of total mucosal area)	Portal venous pressure (cm H_2O)	Mucosal necrosis (% of total mucosal area)
No injection		37±1·6	15±2·5	12±0·9	3±0·5
Saline		38±1·2	16±2·3	12±0·9	3±0·5
Propranolol	5	31±1·6*	8±1·2*	11±0·9	3±0·5
	10	26±3·0**	7±0·6**	12±0·9	4±0·7
	20	25±2·4**	6±0·8**	13±0·3	4±0·8
Nadolol	5	35±0·4	16±3·3	11±0·7	3±0·7
	10	31±0·5**	5±1·1**	11±0·8	3±0·5
Metoprolol	10	37±3·5	9±1·8*	12±0·8	3±0·6
	20	30±2·2*	6±1·1**	11±0·9	2±0·5
Labetalol	20	27±3·9*	8±1·0*	11±0·5	4±0·7
	40	30±1·4**	6±1·2**	12±0·9	3±0·5
Pindolol	3	34±3·3	15±2·9	11±0·4	2±0·4
	6	37±4·3	14±2·7	12±0·8	3±0·6

*$P<0·05$, **$P<0·01$, compared with the saline-injected group. Results are expressed as mean±s.e.m., n=6.

Propranolol (possessing β_1, β_2 and local anaesthetic activity) is the most promising β-adrenoceptor antagonist in reducing portal venous pressure in portal hypertensive rats, reducing the portal venous pressure in all three doses. Nadolol (lacking a local anaesthetic effect) was not as good as propranolol, indicating that the local anaesthetic effect is probably important in reducing the portal venous pressure. Metoprolol (without β_2-antagonism and with a weak local anaesthetic effect) was less effective than propranolol. Labetalol (with an additional α-adrenoceptor antagonizing action but with a weaker local anaesthetic effect) did not seem to have additional benefit on the reduction of portal venous pressure. Pindolol, a β-adrenoceptor antagonist with intrinsic sympathomimetic activity, simply had no effect on the portal vein pressure. This shows that an intrinsic sympathomimetic effect can counteract the β-adrenoceptor blocking action on the portal vein pressure.

Portal vein ligation increased portal venous pressure which was accompanied by a significant increase in gastric mucosal damage. This ethanol-induced gastric mucosal necrosis was significantly reduced by β-adrenoceptor antagonists in portal hypertensive rats, while that of sham-operated rats was unaffected. This difference in action may be due to the fact that the aggravation of ethanol-induced necrosis in portal hypertensive animals is probably caused by an increase in portal vein pressure which was alleviated by β-adrenoceptor antagonists. This may explain why these drugs are only effective as mucosal-protective agents in portal hypertensive rats. Therefore, the aggravation of ethanol-induced necrosis and the mucosal-protective effect of β-adrenoceptor antagonists in portal hypertensive animals are portal venous pressure—rather than systemic pressure—dependent. Furthermore, it was found that the significance of decrease in mucosal necrosis corresponded to the degree of reduction in portal vein pressure but not to systemic blood pressure (Table 3). Therefore, controlling the portal vein pressure in patients with portal hypertension may be a way to reduce the incidence of gastric mucosal damage.

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